REMARKS

Claims 62-63, 71-74, 76-84 and 88-112 are currently pending in the application. Applicants gratefully acknowledge the allowance of claims 95-98. By way of the present amendment, claims 1-89, 93-94 and 106 have been canceled. Claims 90-92, 100, 101-105 and 107 have been amended, and new claims 113-117 have been added.

Accordingly, upon entry of the amendments requested herein, claims 95-105 and 106-117 will be pending. Support for the amendments can be found throughout the specification and claims as originally filed. No new matter has been added.

The claim amendments requested herein should in no way be construed as acquiescence to any of the rejections and have been made solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed and/or prior to amendment herein in this or a separate application(s).

Claim Objections

Claims 81 and 106 have been objected to under 37 CFR §1.75(c), as being of improper dependent form for failing to further limit the subject matter of previous claims 73 and 99, respectively. This rejection is based on the ground that "there is no nexus between the transfection of a nucleic acid molecule encoding a B7-2 molecule in a tumor cell or cells or solid tumor *in vivo* and the inhibition of the invariant chain expression in said cell or said cells of a solid tumor *in vivo* "

Solely to expedite prosecution, claims 81 and 106 have been canceled, thus rendering this objection moot.

Claim Rejections under 35 USC § 112, first paragraph

The rejection of claims 62-63, 71-74, 76-86 and 90-94 for lack of enablement was maintained on the ground that,

> [T]he specification, while being enabling for a method for treating a mammalian subject having **a solid tumor**, comprising **direct injection** into cells of said tumor a nucleic acid encoding [a] B7-2 molecule in a form suitable for expression of the B7-2 molecule in cells of said tumor and wherein **said B7-2 molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand** such that the growth

> of said tumor is inhibited; the same method for modifying a tumor cell *in vivo*, does not reasonably provide enablement for a method of treating a subject with any tumor or a method of modifying any tumor cell *in vivo* to express a B7-2 molecule by transfecting cells of the tumor or the tumor cell with a nucleic acid molecule encoding B7-2 by any route of delivery. (Paper No. 21, page 3, emphasis in original)

Applicants respectfully traverse this rejection. However, solely in the interest of expediting prosecution, claims 62-63, 71-74, 76-86, 88 and 93-94 have been canceled, and claims 90-92 have been amended to depend from an allowed claim. Accordingly, these rejections are now moot.

Notwithstanding the cancellation of these claims, Applicants wish to make the following remarks of record The basis for maintaining the rejection for lack of enablement relies on the assertion that "even several years after the effective filing date of the present application, *in vivo* vector targeting to desired cells remains unpredictable, and therefore therapeutic effects obtained through an effective transgene delivery and expression in target cells also remain unpredictable as evidenced by the teachings of Miller *et al.*, Denarain, Verma *et al.*." (Paper No. 21, page 12).

A detailed discussion of Miller *et al.*, Denarain, and Verma *et al.* has already been made of record. In essence, each of the cited references focuses on the unpredictability and inefficiency of gene therapy in applications where *prolonged and widespread expression of an introduced gene in an individual is required in order to observe a therapeutic benefit* (e.g., for genetic diseases such as cystic fibrosis). This reading of the references has not been disputed. However, while acknowledging that long-term and widespread transgene expression in target tumor cells *is not required for the presently claimed invention*, the Examiner has not presented any additional references or evidence that would sustain this rejection.

The instant specification teaches that a therapeutic benefit is expected even if gene delivery of B7-2 occurs in only a fraction of the tumor cells of the individual, and even if the expression of the B7-2 molecule in the tumor cells is short-lived. The data presented in Examples 2-5 clearly support this teaching by demonstrating that even a small fraction of B7-2 transfected cells produce a sufficient level of B7-2 to trigger an immune response to tumor cells *in vivo* in an accepted mouse model. Moreover, the

specification is not limiting with respect to the number of doses to be delivered, and it is well-known in the art that clinical trials involving gene therapy "have shown few signs of toxicity and no hints of runaway mutations." (Marshal, at page 1054). Thus, *in* vivo delivery of B7-2 molecules into the circulation in a form suitable for expression, as taught by Applicants, would be expected to reach and transfect at least a small fraction of tumor cells. Once delivered, the transfected tumor cells would be expected to produce B7-2 at a level sufficient to elicit an immune response to the tumor cells, and efficacy (e.g., tumor regression, lack of progression, etc.) could be readily monitored by standard methods. The presumption that some cancer cells, e.g., lymphoma, naturally express B7-2 at a level too low to induce any effective T cell anti-tumor response is irrelevant. Such cells, transfected with B7-2 molecules according to the methods of the invention would produce additional B7-2, leading to a level sufficient to elicit the desired response.

Accordingly, further evidence should not be required to demonstrate that the various obstacles referred to by Miller *et al.*, Denarain, and Verma *et al.* are simply not applicable to Applicants' invention. Given the teachings set forth in the specification, one of ordinary skill in the art would conclude that *in vivo* delivery of B7-2 in a form suitable for expression would result in the production of B7-2 at a level sufficient to achieve at least a modest level of therapeutic benefit. A need for additional proof of "a broad range of therapeutic effects encompassing curing or eradicating any tumor in a cancer patient," is simply not the standard by which enablement is determined.

Rejections under 35 U.S.C. §112, first paragraph

Claims 81 and 106 have rejected as lacking essential steps or critical agents recited for modifying a tumor cell or cells *in vivo* in inhibiting the expression of the invariant chain. Claims 81 and 106 have been canceled, thus rendering this rejection moot.

Claims 73 and 99 have been rejected on the ground that the "transfection of a nucleic acid molecule encoding B7-2 molecule in a tumor cell or cells of a solid tumor *in vivo* in claims 73 and 99, respectively, has no effect on inhibiting the expression of the invariant chain." (Paper No. 21, page 15)

Applicants respectfully traverse this rejection with respect to pending claim 99. Claim 99 is directed to a "method for modifying cells of a solid tumor *in vivo* to express a B7-2 molecule, comprising direct injection of a nucleic acid molecule encoding a B7-2 molecule in a form suitable for expression of the B7-2 molecule, into the tumor cells, wherein the B7-2 molecule has the ability to costimulate a T cell and the ability to bind a CD28 or CTLA4 ligand, such that B7-2 is expressed by the tumor cells. Inhibition of the invariant chain is not required by the claimed method. Therefore, Applicants respectfully submit that this rejection is improper and should be withdrawn.

In view of the foregoing, Applicants further request that the objection to claims 100-105 and 107-112 as being dependent on rejected claim 99, also be withdrawn.

Claim 89 has been rejected on the ground that there is insufficient antecedent basis for the phrase "the nucleic acid molecule." Claim 89 has been canceled, thus rendering this rejection moot.

CONCLUSION

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
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